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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/095,639	06/11/1998	PAOLO POZZILLI	515-4111	9860

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/095,639	Applicant(s) POZZILLI, PAOLO	
	Examiner Thaian Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Applicants' Amendment, filed 4/8/2002, Paper No. 15, has been entered.

Claims 21-27 have been canceled. Remarks that are pertinent to the newly added claims that were filed in response to the Office Action mailed on November 22, 1999 (Paper No. 7) will be addressed in present Office Action.

Claims 28-36 are pending and under current examination.

Any rejection made of record in the prior Office action, mailed 9/28/01, Paper No. 13, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Claim Rejections - 35 USC § 101

The prior rejection of the claims 21-27 under 35 USC 101 is withdrawn in view of Applicants' cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention. The reasons for the rejection of these claims are advanced in the prior Office action, mailed 9/28/01, Paper No. 13, pages 3-8.

The claimed invention is directed to dietary or pharmaceutical products for the prevention of insulin-dependent diabetes, said product comprising at least one modified bovine beta-casein or fragments thereof selected from the group consisting of recombinant or synthetic caseins which do not contain SEQ ID NOS 1 and 2 and methods for the prevention IDDM.

The specification teaches that in genetic variants of bovine β-casein, it has been found that a particular hexapeptide sequence elicits an immune response by the production of anti-β-casein antibodies and lymphocytes which recognize such sequences (see p. 2, lines 9-13). The specification further teaches that the presence of these this hexapeptide sequence which is common to both bovine β-casein and human GLUT 2 in infant formula may cause an immune response where anti-bovine β-casein antibodies recognize GLUT 2 on insulin producing cells. This immune response is thought to lead to onset of insulin-dependent diabetes (see p. 2, lines 13-23). The specification teaches a product derived from milk which is free of non-human β-casein, a product derived from milk comprising at least one β-casein modified from non-human mammals without the hexapeptide sequence, as well as methods, such as the administration through infant formula, of using the product for the prevention of insulin-dependent diabetes (see pp. 5-6 of the instant

specification). The specification specifically teaches that the separation of β-casein from acid casein by ion-exchange chromatography (see Example 1), and that the product is then analyzed by chromatography to evaluate the absence of β-casein (see Example 2). The specification further teaches that the product can be purified by diafiltration and lyophilization (see Example 3).

Applicants argue that, in the prior Office action, the Examiner's contention with regard to an unreasonable amount of experimentation have nothing to do with the directions for the use of the claimed invention, that the invention is a food for newborns and infants and since the prior art methods of feeding casein-based food to newborns and infants is completely analogous to the feeding of the modified caseins of the present invention, no undue experimentation is required to use the claimed invention [see p. 5, last full paragraph]. Further, Applicants argue that the Examiner's enablement rejection is based upon 35 USC 101, where the Examiner is calling for proof that the claimed invention is effective in preventing diabetes, and that all that is required under 35 USC 101 is that some beneficial function flow from the disclosure, and as such, there can be no valid "how to use" objection in the claimed subject matter [see pp. 5-6, bridging paragraph].

In response, it is noted that the prior rejection of the claimed subject matter under 35 USC 101 is <u>not</u> directed to a utility rejection, but because the claimed invention is directed to non-statutory subject matter, and in particular, naturally occurring milk [see pp. 2-3 of the prior Office action]. Additionally, it is noted that

the 35 USC 101 rejection has been withdrawn in view of Applicants' amendments. Further, with regard to the claimed products and methods of the instant invention, Applicants argue that the products are intended for "nutritional" use [see p. 6, 1st paragraph], however, the claims as written, as directed to products and methods which are for the prevention of IDDM and not for providing nutrition to the host. As such, the prior rejection, with regard to enablement, is maintained. This is because the specification fails to teach that administration of the product would provide prevention of insulin-dependent individual in any individual. The Examiner cites Cavallo *et al.* to show that although β-casein may be a good candidate milk protein related to the pathogenesis IDDM, neither the state of the art, nor the specification provide teachings to show with particularity that evidence of consumption of milk without non-human β-casein would indeed prevent diabetes. Furthermore, the Examiner has presented the unpredictable state of the art with particular regard to various factors that could be potentially involved in the pathogenesis of IDDM [see Atkinson, cited in the prior Office action pp. 5-6], and as such in view in of the quantity of experimentation necessary to determine the parameters listed above for achieving prevention of IDDM, the lack of direction or guidance provided by the specification to carry out prevention of IDDM in any individual, the lack of working examples, as well as the unpredictable state of the art with regard to the hypothesis of an autoimmune mechanism for IDDM, it would

have required undue experimentation for one skilled in the art to make and/or use the claimed invention and methods of using the same.

Applicants argue that in the medical art, the question of prevention does not require a showing that non-exposure to a potentially dangerous substance does not produce damage, and further, that when the hypothesis is made that a substance can induce or provoke an affliction, based on documented epidemiological studies which indicate that such a substance could be harmful, the first remedy to be taken is to find an effective means to prevent the exposure to said substance. Applicants argue that the present application teaches an effective means for preventing exposure to a diabetogenic substance which is useful even if 100% prevention of IDDM is achieved. Applicants further argue that Atkinson *et al.* do not state that the removal of immunogenic hexapeptide sequences from non-human beta-casein is counterproductive in preventing IDDM [see Response, pp. 6-7].

It is noted, as stated *supra*, that the Examiner does not dispute that the claimed means for preventing exposure to a diabetogenic substance would not be *useful*; however, the rejection presented by the Examiner is directed to the lack of teachings, guidance or examples by the specification to show that administration of the claimed product would indeed prevent IDDM in any individual. Furthermore, when taken with the state of the art of the pathogenesis of IDDM [see *supra*], it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention and methods of using the same.

Applicants present recent references showing the state of the art with regard to the present view of the cow's milk hypothesis as the cause of IDDM and wish the Examiner to consider the statements presented by Applicants [see p.7 of the Response]. Applicants state that they do not take issue with the hypothesis presented by Atkinson *et al.*, that several environmental factors may be implicated in the pathogenesis of IDDM, however, exposure to cow's milk, and in particular, exposure to beta casein fractions is the most common agent to which susceptible individuals are exposed. Applicants further argue that the Examiner has confused two separate issues, firstly, that there may be many potential factors involved in the pathogenesis of IDDM, and that whether it can be predictably concluded that beta-casein causes the observed immune response in humans [see p. 8 of the Response].

The references provided by Applicants have been considered however, they are not found persuasive. The Examiner reiterates, as *supra*, that the present rejection of the claimed invention is directed to the lack of teachings, guidance or working examples provided by the specification for the showing that administration of the claimed dietary product would prevent IDDM in an individual; particularly because the pathogenesis of IDDM has not yet been resolved in the state of the art [as provided by Atkinson *et al.*], as well as the conjecture, but not statement of fact, that beta casein is a candidate protein that is implicated in the pathogenesis of IDDM [as stated by Cavallo *et al.*]. Applicants state that the references provided

disclose that more than half of diabetic patients showed an immune response to beta-casein derived from cow's milk, and that even whereas Type 1 diabetes is a multi-factorial disease, this 51.1% finding is persuasive evidence implicating the role of cow's milk and beta-caseins response involving cross reaction with the insulin-producing cells in the pancreas, which leads to the destruction of insulin producing cells [see p. 8, 3rd paragraph]. The Examiner argued in the prior Office action that the claim drawn to a product with non-human beta casein substituted with homologous sequence of human beta-casein, it would be expected that the hexapeptide sequence would also elicit an immune response. Applicants argue that the present application does not teach the human and non-human sequences are homologous, or that the human beta-caseins elicit an immune response in humans. Applicants state that attached to the Amendment are published scientific papers, which indicate that cow's milk consumption is positively correlated with Type 1 diabetes incidence. Applicants further state that attached to the Amendment is a declaration signed by the inventor, Paolo Pozzilli, which provides evidence that lymphocytes from type 1 diabetics show reactivity to beta-casein which cross-reacts with the beta-cell antigen GLUT 2 [see p. 9, paragraphs 2-3].

The references provided by Applicant have been considered, however, they are not found persuasive because Applicants have not provided teachings or guidance to show that the pathogenesis of IDDM is directly implicated with the exposure of the beta-casein sequence as claimed. For example, Tullin *et al.* [**Journal**

of Immunology, 1997 June 1;158(11):5554-9] study spontaneously diabetic BB rats. In particular, Tullin *et al.* discuss that the diabetes-prone Bio-Breeding (DP-BB) rat spontaneously develop IDDM and that this rat model closely resembles the human disease [see p. 5554, 1st column and *Abstract*]. Note that it would not be expected that these rats would have been exposed to cow's milk at any time during their life, and as such, the pathogenesis of their spontaneously-developed IDDM would not rely upon exposure to the beta-caseins contained in the cow's milk, as asserted by Applicants.

Accordingly, when taken with the state of the art of the pathogenesis of IDDM [see *supra*], as well as the lack of teachings, guidance or working examples provided by the specification for the showing that administration of the claimed dietary product would prevent IDDM in an individual; it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-36 are drawn to methods for preventing insulin-dependent diabetes, but the claims fail to recite appropriate process steps detailing how to prevent insulin-dependent diabetes. For example, in claims 33-36, it is not clear how the administration of a product relates to the preamble, "A method for preventing insulin-dependent diabetes." Furthermore, claim 36 recites a method by obtaining the recombinant human beta casein by cloning methods; however, the claim recites no steps involving gene expression.

Claim Rejections - 35 USC § 102

The prior rejection of claims 21-27 under 35 USC 102(b) is withdrawn in view of Applicants' cancellation of the claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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